Remarks

Applicants have amended claims 1, 54, 59, 60, and 78.
Applicants have cancelled claims 52 and 53.
Applicants have withdrawn claims 50, 56-58, 62, 70, 74-77, 81, 88-91, 99, and 103-139.

Support for the amendments to claim 1 are to be found in the specification at page 4, lines 23, 24, and 27 ("carbohydrate moiety", "monosaccharide", amino sugar"), and at page 6, lines 23-25 ("amide bond"), and in original claims 52 and 53 (both now cancelled).

Applicants have amended claims 54, 59, 60, and 78 to conform to U.S. English spelling

Election/Restrictions

1) The Examiner acknowledged Applicants' election of Group I (claims 1, 48-73, 78-87, and 92-102) and the election of the following species: carboxylic terminated PANAM dendrimer generation 3.5-glucosamine, glucosamine-6-phosphate (*sic*) and severe sepsis.

Applicants respectfully note that their provisional election of species was to the carbohydrate species of glucosamine 6-sulphate (claim 60) and not to a glucosamine-6-phosphate as stated by the Examiner in the instant Office action. See page 3, last paragraph, of Applicants response to the restriction requirement and election of species, filed 3 March 2009 and also in the Examiner's Communication mailed February 4, 2009, at page 3, third paragraph. Applicants believe this to be a typographical error by the Examiner and request confirmation by the Examiner that glucosamine 6-sulphate is under examination.

Applicants affirm the provisional election of product species as recited above having the moiety as claimed (sulphate) as stated above.

2) The Examiner then stated that the categories the claims of Groups I-IV encompassed were "product, method of using in vivo, method of making, and method of using in vitro" and that accordingly, Groups I-IV are not linked by the same or a corresponding technical feature so as to form a single general inventive concept.

Applicants respectfully submit that the above categories as recited appear to be elements of a single category as disclosed by the Examiner's recitation of 37 CFR 1.475 at (b)(3), viz. (a)

product (Group I), a process specially adapted for the manufacture of the said product (Group III), and the use of the said product (Groups II and IV). Therefore Applicants request that, if the claims under consideration are found allowable, the Examiner examine the other claimed Groups.

The Examiner further stated that Groups I-IV lack the same or corresponding special technical features for the following reasons: the technical feature linking the claims is a glycodendrimer and that prior art exists which causes the glycodendrimer in the instant application to lack a special technical feature. The Examiner stated that glycodendrimer has been previously disclosed in Rockendorf et al. (2001, Topics in Curr. Chem,, 217: 213, Figure 7). Therefore, the Examiner continued, the feature linking the claims does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art.

Applicants respectfully submit that claim 1 as originally filed recited "(a) glycodendrimer comprising carbohydrate moieties covalently linked to a carboxylic terminated dendrimer." Applicants submit that dendrimers are well known, and it is known that saccharides can be attached to dendrimers. However, the established practice has been to link the saccharides to amine terminated dendrimers, as disclosed by Applicants in the Specification at page 3, lines 12-19. Numerous examples of literature references to such processes are contained in the present specification as filed (see IDS reference nos. 3 (Newkome et al.), 4 (Jansen et al.), 5 (Pagé and Roy), 6 (Ashton et al.), and 7 (Malik et al.) for example).

Rockendorf et al. is a review of glycodendrimers that focuses on the molecular architectures of glycodendrimers and the principal design strategies for their preparation. It teaches various types of glycodendrimer including those examples highlighted by the Examiner: carbohydrate-functionalised cationic PAMAM dendrimers (for example, where the terminal amine groups are reacted with a disaccharide lactone or isothiocyanato derivative, see page 214 of Rockendorf et al.), and an example comprising a lysine-derived dendrimer linked to modified N-acetyl-glucosamine via reaction of thiol groups on the sugar with terminal α-chloroacetyl groups (Rockendorf et al. at page 209).

Regarding groups suitable for dendrimer functionalisation, Rockendorf et al. teaches that sugar derivatives containing functional groups including thiols, isothiocyanates or Michael acceptors may be conjugated to dendrimers, often via indirect connection through a spacer group. However, there is no teaching in Rockendorf et al. of a glycodendrimer in which an amino sugar

is covalently linked to a carboxylic terminated dendrimer by an amide bond between the amine group and a dendrimer carboxylic group.

Therefore, Applicants respectfully submit that Rockendorf et al. do not teach the glycodendrimers as originally claimed and that the feature linking the claims constitutes a special technical feature as defined by PCT Rule 13.2.

Nevertheless, to advance prosecution of the claims under consideration, Applicants provisionally consent to examination of claims 1, 48-73, 78-87, and 92-102.

3) The Examiner has withdrawn claims 50, 56-58, 62, 70, 74-77, 81, 88-91, 99, and 103-139 from further consideration pursuant to 37 C.F.R. § 1.142(b), there being no allowable generic or linking claim. The Examiner stated that claims 1, 48-49, 51-55, 59-61, 71-73, 78-80, 82-87, 92-98, and 100-102.

Applicants request that, if the claims under consideration are found allowable, the Examiner examine the other claimed species recited in claims 50, 56-58, 62, 70, 74-77, 81, 88-91, 99, and 103-139.

Claim Objections

4) The Examiner has objected to the spelling of the terms "sulphated" in claim 54 and "sulphate" in claims 59-60 and 78 and requested they be corrected to "sulfated" in claim 54 and "sulfate".

Applicants respectfully submit that the claims were drafted in the United Kingdom where the spelling of the terms "sulphated" and "sulphate" are correct. Nevertheless, in order to advance prosecution, Applicants have amended the claims as requested by the Examiner to conform to American English spelling.

Rejections under 35 USC § 112, 1st Paragraph

5) The Examiner has rejected claims 1, 48-49, 51-55, 59-61, 63-69, 71-73 under 35 USC § 112, 1st paragraph, as lacking written description.

The Examiner stated that Applicants provided no description of the claimed generic glycodendrimer, either in word, structure, by formula, by chemical name, of by physical properties that would indicate that Applicants were in possession of the claimed generic glycodendrimer at the time of the invention.

6) Applicants have amended claim 1 to recite "A glycodendrimer comprising monosaccharide carbohydrate moieties covalently linked to a carboxylic terminated dendrimer, wherein the monosaccharide carbohydrate moiety is an amino sugar and whereby the amine group of the amino sugar forms an amide bond with the carboxylic group of the carboxylic terminated dendrimer".

Applicants submit that the specification disclosed structural features of the claimed generic glycodendrimer in word by the physical and chemical properties of the genus and which would have reasonably conveyed to one of skill in the art that the inventors, at the time the invention was made, had possession of the claimed invention.

Applicants submit that claim 1 as amended recites that the carbohydrate moieties are monosaccharides each being an amino sugar, and are clearly defined in terms of their structural characteristics. Applicants submit that the structure of amino sugars are well known to thosxe of skill in the art. Representative species of amino sugars are also described in the specification for example, glucosamine, mannosamine or galactosamine, which also indicates that the amino sugar may be derivatised or modified (for example, sulfated, acetylated) (see page 4, lines 28-34 and continued on page 5, lines 1-9).

The dendrimer component is also defined by its structural characteristics, in that it is carboxylic-terminated. Different types of dendrimer are disclosed at page 1, lines 23-33 of the specification, such as, (poly(amidoamine) (PAMAM) and poly(propyleneimine) (DAB) dendrimers), and carboxylic terminated dendrimers of these types are known from the prior art (see Malik *et al*, IDS reference no. 7, at page 137). The use of half generation nomenclature

(1.5, 2.5 etc.) to characterise generations of dendrimers having carboxylic groups is also well known (see Malik *et al*, IDS reference no. 7, at page 135).

Applicants also submit that Rockendorf et al. (2001, Topics in Curr. Chem., 217: 201-238) do not teach a glycodendrimer having the physical and chemical properties as claimed.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 1, 48-49, 51-55, 59-61, 63-69, 71-73 under 35 USC § 112, 1st paragraph as lacking written description.

7) The Examiner has rejected claims 1, 48-49, 51-55, 59-61, 63-69, 71-73, 78, 80, 82-87, 92-98, and 100-102 as lacking enablement.

The Examiner stated that specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The Examiner stated that *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404, the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Regarding Wands factors (1) and (2), the Examiner stated that the claims are drawn to a generic glycodendrimer comprising carbohydrate moieties linked to carboxylic terminated dendrimer. The Examiner then stated that the term "glycodendrimer" encompasses carbohydrate-containing molecules which can be grown generationwise following an iterative repetitive synthesis and there are various types of dendrimers depending upon their repetitive base molecule. In addition, the Examiner continued, carbohydrate moiety attached to the dendrimers encompasses disaccharide, trisaccharide, oligosaccharide, and polysaccharide as well as monosaccharide; thus the number of theoretically conceivable glycodendrimers as claimed is in the millions rendering the scope of the claim large.

> "[T]he applicant does not have to utilize and particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognise that [he or she] invented what is claimed'" *In re Alton*, 37 USPQ 2d 1578, 1581 (CAFC 1996) quoting *In re Gosteli*, 872 F.2d 1008, 1012; 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989).
>
> An invention does not have to be described *ipse verbis* in order to satisfy the description requirements of 35 USC section 112. In re Lukach, 169 USQP 795 (CCPA 1971).

8) Applicants have amended claim 1 to recite "A glycodendrimer comprising monosaccharide carbohydrate moieties covalently linked to a carboxylic terminated dendrimer, wherein the monosaccharide carbohydrate moiety is an amino sugar and whereby the amine group of the amino sugar forms an amide bond with the carboxylic group of the carboxylic terminated dendrimer.

Applicants respectfully submit that the scope of claim 1 no longer encompasses glycodendrimers derived from di-, tri-, or oligo-saccharides, saccharides that do not contain an amino group, or dendrimers which are not carboxylic-terminated. The number of theoretically conceivable glycodendrimers is therefore relatively low and the breadth of the claims thus limited. The skilled person would be able to produce those glycodendrimers falling within the scope of the claims as discussed above without undue experimentation, and the claims are thus enabled.

9) Regarding Wands factor (3), the Examiner stated that Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the instant composition for accomplishing the desired result of the claimed invention without undue experimentation.

> "[T]he applicant does not have to utilize and particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognise that [he or she] invented what is claimed'" *In re Alton*, 37 USPQ 2d 1578, 1581 (CAFC 1996) quoting *In re Gosteli*, 872 F.2d 1008, 1012; 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989).
>
> An invention does not have to be described *ipse verbis* in order to satisfy the description requirements of 35 USC section 112. In re Lukach, 169 USQP 795 (CCPA 1971).

10) Applicants respectfully submit that support for tests that are highly predictive for the pharmaceutical use for the instant composition are disclosed in the specification at pages 21-24 (Example A4: "Toxicity in Human Cerll Lines"; Example A5: "Toxicity of Compounds Against Primary Human Cells in vitro"; Example A6: "The Effect of Dendrimer.....on the Release of MIP-1β from Single Donor, Human PBMN Cell, MDMs and Peritoneal Macrophages"). Applicants submit that additional evidence to support the pharmaceutical us of the instant composition is to be found in the Examples from pages 24 through 60 that disclose many different assays of biological and pharmacological activity (*in vitro* and *in vivo*) and relevance to pharmaceutical use.

Applicants further submit the specification discloses that the glycodendrimers of the present invention possess unexpected properties, notably immuno-modulatory activities that give them anti-inflammatory properties. The glycodendrimers downregulate the immune system by inhibiting the release of chemokines including MIP-1β, MIP-1α, and IL-8 (see page 15, line 13-17). Supporting data is also provided for dendrimer generation 3.5 glucosamine and dendrimer generation 3.5 glucosamine sulfate in the specific examples. The skilled person would be able to produce those glycodendrimers falling within the scope of the claims as discussed above without undue experimentation, and the claims are thus enabled.

11) Regarding Wands factor (4), the Examiner stated that Malik et al. teach that dendrimers can have differing cytotoxic, haemolytic or bio-distribution properties (Applicants' emphasis).

> "[T]he applicant does not have to utilize and particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognise that [he or she] invented what is claimed'" *In re Alton*, 37 USPQ 2d 1578, 1581 (CAFC 1996) quoting *In re Gosteli*, 872 F.2d 1008, 1012; 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989).
>
> An invention does not have to be described *ipse verbis* in order to satisfy the description requirements of 35 USC section 112. In re Lukach, 169 USQP 795 (CCPA 1971).

12) As with Applicants' comments to the Examiner's discussion of Wands factor (3), Applicant notes that Malik et al. contains no teaching regarding the immuno-modulatory properties of glycodendrimers, and thus cannot be relied upon to inform as to the anti-inflammatory properties of such compounds.

The specification teaches that the observed anti-inflammatory properties may be due to the glycodendrimers acting as polyvalent binding inhibitors of the immunoregulatory functions of dendritic cells and of lymphocytes (see specification at page 10, lines 14-19). It also teaches that the glycodendrimers of the invention are large molecules and therefore accumulate more rapidly in areas of inflammation than in normal tissue (see page 13, lines 18-22). The skilled person would understand that large molecule glycodendrimers other than the specific generation 3.5 examples would accumulate in areas of inflammation, and that glycodendrimers comprising amino sugars other than modified or unmodified glucosamine would also act as polyvalent binding inhibitors, possessing similar immuno-modulatory activities and anti-inflammatory properties. The skilled person would be able to produce those glycodendrimers falling within the scope of the claims as discussed above without undue experimentation, and the claims are thus enabled.

13) Regarding Wands factors (6) and (7), the Examiner stated that the only disclosed working example of dendrimer and carbohydrate moiety is a carboxylic terminated poly(amidoamine) dendrimer (PAMAM) generation 3.5 and glucosamine or modified glucosamine such as glucosamine-6-sulfate in the specification (Fig.1b). However, the Examiner continued, they are not representative of species falling within the scope of the claimed genus as stated above. The Examiner stated that there is no example concerning disaccharide, trisaccharide, oligosaccharide, and polysaccharide as carbohydrate moiety other than glucosamine or modified glucosamine.

> "[T]he applicant does not have to utilize and particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognise that [he or she] invented what is claimed'" *In re Alton*, 37 USPQ 2d 1578, 1581 (CAFC 1996) quoting *In re Gosteli*, 872 F.2d 1008, 1012; 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989).
>
> An invention does not have to be described *ipse verbis* in order to satisfy the description requirements of 35 USC section 112. In re Lukach, 169 USQP 795 (CCPA 1971).

14) Applicants submit that claim 1 as amended now recites "A glycodendrimer comprising monosaccharide carbohydrate moieties covalently linked to a carboxylic terminated dendrimer, wherein the monosaccharide carbohydrate moiety is an amino sugar and whereby the amine group of the amino sugar forms an amide bond with the carboxylic group of the carboxylic terminated dendrimer". Applicants submit that the working example of glucosamine or modified glucosamine would enable one of skill in the art to make and use other types of glycodendrimers comprising a monosaccharide such as glucose, mannose, galactose, mannosamine, galactosamine

and derivatives thereof as disclosed in the specification at page 4, lines 28-34, and at page 5, lines 6-15 and also in dependent claim 54. The skilled person would be able to produce those glycodendrimers falling within the scope of the claims as discussed above without undue experimentation, and the claims are thus enabled.

15) Regarding Wands factor (8), the Examiner stated that because of the known unpredictability of the art (as discussed by the examiner earlier) and in the absence of experimental evidence commensurate in scope with the claims, one of ordinary skill in the art would be presented with an unpredictable amount of research effort to identify a glycodendrimer out of the plethora of possibilities encompassed by the instant claims that would have the desired biological properties.

> "[T]he applicant does not have to utilize and particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognise that [he or she] invented what is claimed'" *In re Alton*, 37 USPQ 2d 1578, 1581 (CAFC 1996) quoting *In re Gosteli*, 872 F.2d 1008, 1012; 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989).
>
> An invention does not have to be described *ipse verbis* in order to satisfy the description requirements of 35 USC section 112. In re Lukach, 169 USQP 795 (CCPA 1971).

16) Applicants have amended Claim 1 to recite "A glycodendrimer comprising monosaccharide carbohydrate moieties covalently linked to a carboxylic, wherein the monosaccharide carbohydrate moiety is an amino sugar and whereby the amine group of the amino sugar forms an amide bond with the carboxylic group of the carboxylic terminated dendrimer".

Applicants respectfully submit that a process for the synthesis of the claimed glycodendrimers by covalently linking the amine group of the amino sugar to the carboxylic-terminated dendrimer in the presence of a coupling agent is described at page, lines 7-25 of the specification, and in the specific examples (for example, Example A1 on pages 16-18). The process facilitates the preparation of multiple glycodendrimers having glucosamine, glucosamine 6-sulfate, glucosamine 3,6-disulfate and glucosamine 3,4,6-trisulfate as the carbohydrate moiety, and could readily be applied without undue experimentation by the skilled person to link other carboxylic-terminated dendrimers and amino sugars.

The glycodendrimers of the present invention also possess unexpected properties, notably immuno-modulatory activities that give them anti-inflammatory properties. They downregulate the immune system by inhibiting the release of chemokines including MIP-1β, MIP-1α, and IL-

8 (see specification at page 15, line 13-17). Supporting data is also provided for dendrimer generation 3.5 glucosamine and dendrimer generation 3.5 glucosamine sulfate in the specific examples. The Examiner has commented that Malik et al. teaches that dendrimers can have differing cytotoxic, haemolytic or bio-distribution properties. However, that document contains no teaching regarding the immuno-modulatory properties of glycodendrimers, and thus cannot be relied upon to inform as to the anti-inflammatory properties of such compounds.

The specification teaches that the observed anti-inflammatory properties may be due to the glycodendrimers acting as polyvalent binding inhibitors of the immunoregulatory functions of dendritic cells and of lymphocytes (see page 10, lines 14-19). It also teaches that the glycodendrimers of the invention are large molecules and therefore accumulate more rapidly in areas of inflammation than in normal tissue (see page 13, lines 18-22). The skilled person would understand that large molecule glycodendrimers other than the specific generation 3.5 examples would accumulate in areas of inflammation, and that glycodendrimers comprising amino sugars other than modified or unmodified glucosamine would also act as polyvalent binding inhibitors, possessing similar immuno-modulatory activities and anti-inflammatory properties. The skilled person would be able to produce those glycodendrimers falling within the scope of the claims as discussed above without undue experimentation, and the claims are thus enabled.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 1, 48-49, 51-55, 59-61, 63-69, 71-73, 78, 80, 82-87, 92-98, and 100-102 under 35 USC § 112, 1st paragraph as lacking enablement.

Rejections under 35 USC § 103(a)

17) The Examiner has rejected claims 1, 48-49, 51-55, 59-61, 63-69, 71-73, 78-80, 82-87, 92-98, and 100-102 as being unpatentable over Rockendorf et al. (Topics in Current Chemistry 217: 201-238, 2001) in view of Malik et al. (J. Controlled Release 65: 133-148, 2000) and US Publ. No. 2003/0114418 (effective filing date 14 Feb 2001).

The Examiner stated that Rockendorf et al. teach glycodendrimers, sugarcoated non-carbohydrate dendrimers, multivalent glucodendrimers, and cationic polyamidoamine (PAMAM) dendrimer functionalized (covalently linked) with carbohydrate moiety in the periphery and N-acetyl-glucosamine-functionalized dendrimers.

The Examiner stated that reference differs from the instant claims insofar as it does not specifically teach glucosamine 6-sulfate linked to PAMAM generation 3.5 and the concentration of glycodendrimer.

The Examiner then stated that Malik et al. teach that dendrimers are highly branched macromolecules of low polydispersity and disclosed several dendrimers including amine terminated PAMAM dendrimers (generation 1-4) and carboxylic acid terminated PAMAM dendrimer (generation 1.5, 2.5, 3.5, 5.5, 7.5. and 9.5).

The Examiner stated that US 2003/0114418 teaches a method of treating inflammation or inflammation-associated disorder by administering glucosamine (or a modified glucosamine) with cyclooxygenase 2-selective inhibitor.

The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use carboxylic terminated PAMAM dendrimer generation 3.5 taught by Malik et al. as a drug delivery carrier of glucosamine derivatives such as glucosamine 6-sulfate in order to make a non-cytotoxic and biocompatible glycodendrimer. The skilled artisan would have been motivated to modify the glycodendrimer taught by Rockendorf et al. by using PAMAM dendrimers bearing carboxylic termini. In addition, the Examiner continued, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute any glucosamine derivative such as glucosamine 6-sulfate for N-acetyl-glucosamine since they are well known to be functional equivalent as taught by US 2003/0114418.

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).
>
> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention.. .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).
>
> "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present

> a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)
>
> "A prima facie case of obviousness can be rebutted by evidence of unexpected results." *In re Merck & Co.*, 231 USPQ 375, 380 (CAFC 1986).
>
> "Factors including unexpected results, new features, solution of a different problem, novel properties, are all considerations in the determination of obviousness in terms of 35 U.S.C. § 103." *In re Wright*, 6 USPQ2d 1959, 1962 (CAFC 1988).

18) Applicants have amended claim 1 to recite "A glycodendrimer comprising monosaccharide carbohydrate moieties covalently linked to a carboxylic terminated dendrimer, wherein the monosaccharide carbohydrate moiety is an amino sugar and whereby the amine group of the amino sugar forms an amide bond with the carboxylic group of the carboxylic terminated dendrimer.

Applicants submit that dendrimers are well known, and it is known that saccharides can be attached to dendrimers. However, the established practice has been to link the saccharides to amine terminated dendrimers. Numerous examples of literature references to such processes are contained in the present specification as filed.

Rockendorf et al. is a review of glycodendrimers that focuses on the molecular architectures of glycodendrimers and the principal design strategies for their preparation. It teaches various types of glycodendrimer including those examples highlighted by the Examiner: carbohydrate-functionalised cationic PAMAM dendrimers (for example, where the terminal amine groups are reacted with a disaccharide lactone or isothiocyanato derivative, see Rockendorf et al. at page 214), and an example comprising a lysine-derived dendrimer linked to modified N-acetyl-glucosamine via reaction of thiol groups on the sugar with terminal α-chloroacetyl groups (Rockendorf et al. at page 209).

Regarding groups suitable for dendrimer functionalisation, Rockendorf et al. teaches that sugar derivatives containing functional groups including thiols, isothiocyanates or Michael acceptors may be conjugated to dendrimers, often via indirect connection through a spacer group. However, there is no teaching in Rockendorf et al. of a glycodendrimer in which an amino sugar is covalently linked to a carboxylic terminated dendrimer by an amide bond between the amine

group and a dendrimer carboxylic group. Applicants therefore submit that differences exist between the scope and content of the prior art and the claims at issue.

Applicants further submit that the compositions of the invention possess secondary factors, including showing unexpected results, solution of a different problem, and novel properties that were not predicted by the state of the art at the time the invention was made. The glycodendrimers of the present invention possess unexpected immuno-modulatory activities that give them anti-inflammatory properties, thereby downregulating the immune system by inhibiting the release of the chemokines MIP-1β, MIP-1α, and IL-8, and the cytokines TNF-α, IL-β and IL-6. Whilst Rockendorf et al. mentions that protein-carbohydrate complexation is important in a wide range of medically significant interactions including, amongst others, inflammation, it also states that the physical chemistry of the effects observed are far from being fully understood, and that the biology of the discussed glycodendrimers is only touched on (page 207). Further, Rockendorf et al. state that "Most of the possibilities of carbohydrate-centred dendrimers still await exploration" (page 233, paragraph 3), and "Moreover, it can be assumed that the potential of carbohydrate-containing dendrimers has by far not been fully exploited as with regard to their possible usefulness as selectively functionalised carrier molecules and their value in supramolecular chemistry and in material sciences. From the point of view of molecular design, many options for glycodendrimer architectures are still awaiting "materialisation"." (page 235, paragraph 2). Rockendorf et al. would not lead the skilled person to expect that glycodendrimers comprising monosaccharide amino sugar moieties covalently linked to a carboxylic terminated dendrimer would have useful immuno-modulatory activities that gives them anti-inflammatory properties. Applicants therefore submit that differences exist between the scope and content of the prior art and the claims at issue.

Malik et al. discloses a study wherein basic biological properties of cationic and anionic dendrimers were examined, and teaches that carboxylic terminated dendrimers were neither haemolytic nor cytotoxic up to concentration levels of 2 mg/ml whereas amino terminated dendrimers were generally cytotoxic and displayed concentration- and generation-dependent haemolysis. However, as mentioned above in the comments above regarding enablement, Malik et al. is silent regarding the immuno-modulatory and anti-inflammatory properties of glycodendrimers. Applicants therefore submit that differences exist between the scope and content of the prior art and the claims at issue.

If the skilled person were motivated to combine the teaching of Malik et al. with that of Rockendorf et al., they would not arrive at the subject matter of the present claims, as Rockendorf et al. does not teach that monosaccharide amino sugars are suitable for direct functionalisation of carboxylic terminated dendrimers. Instead, as Malik et al. teaches that introduction of amine functionality into anionic dendrimers was required to facilitate further functionalisation of the dendrimer (by reacting with ethylenediamine, see page 138), the skilled person would be led to similarly modify the terminal carboxylate groups of an anionic dendrimer to provide an amine group suitable for further functionalisation with a carbohydrate derivative (for example, by reaction with a disaccharide lactone or isothiocyanato derivative as taught by Rockendorf et al.).

US2003/0114418 teaches a method of treating pain, inflammation or an inflammation related disorder by the administration of glucosamine and a COX-2 inhibitor, and further teaches that the glucosamine may be obtained from sources such as glucosamine sulfate and N-acetyl glucosamine. However, US2003/0114418 is silent about the effect of covalently linking the glucosamine source to moieties such as dendrimers on immuno-modulatory and anti-inflammatory activities, and contains no teaching regarding methods by which the resulting glycodendrimers might be prepared. Thus, the skilled person would not have any expectation from combining the teaching of US2003/0114418 with that of Rockendorf et al. or Malik et al. that a glycodendrimer comprising monosaccharide amino sugar moieties covalently linked to a carboxylic terminated dendrimer would have interesting immuno-modulatory activities and anti-inflammatory properties. Applicants therefore submit that differences exist between the scope and content of the prior art and the claims at issue.

In summary, there is no teaching in any of the cited documents, either alone or in combination, that would lead the skilled person to arrive at the subject matter of the present claims, and the invention has an inventive step.

Applicants submit that the prior art and the claims at issue are different and therefore that claims 1, 66, 85 are not unpatentable over Rockendorf et al. in view of Malik et al. and US Publ. No. 2003/0114418. Applicants further submit that dependent claims 48-49, 51-55, 59-61, 63-65, 67-69, 71-73, 78-80, 82-84, 86, 87, 92-98, and 100-102 are therefore also not unpatentable over Rockendorf et al. in view of Malik et al. and US Publ. No. 2003/0114418.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 1, 48-49, 51-55, 59-61, 63-69, 71-73, 78-80, 82-87, 92-98, and 100-102 under 35 USC § 103(a).

CONCLUSION

With these arguments, Applicants believe that the application is in condition for allowance. If the US Patent Office believes that communication would further the prosecution of this application, then the appropriate US Patent Office personnel are invited to contact the Applicants' below-signed representative at their earliest convenience.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Bell & Associates Deposit Account No. 50-3194.

Respectfully submitted,

Date: 26th October 2009

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